Midlife Cardiovascular Health and Robust Versus Frail Late-Life Status: The Atherosclerosis Risk in Communities Study

Priya Palta, PhD, MHS,[1,*,†] Michael Griswold, PhD,[2] Radhikesh Ranadive, MS,[2] Karen Bandeen-Roche, PhD,[3] Aaron R. Folsom, MD,[4] Natalia Petruski-Ivleva, PhD,[5] Sheila Burgard, MS,[6] Anna Kucharska-Newton, PhD,[7,8,†] and B. Gwen Windham, MD, MHS[2]

[1]Departments of Medicine and Epidemiology, Columbia University Irving Medical Center, New York, New York, USA. [2]The MIND Center, Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA. [3]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. [4]Divison of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota, USA. [5]Sanofi, Cambridge, M assachusetts, USA. [6]Collaborative Studies C oordinating Center, Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [7]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, Carolina, USA. [8]Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, Kentucky, USA.

*Address correspondence to: Priya Palta, PhD, MHS, Departments of Medicine and Epidemiology, Columbia University Irving Medical Center, 622 West 168th Street, PH9 Center Room 212, New York, NY 10032, USA. E-mail: pp2464@cumc.columbia.edu

[†]Authors contributed equally to this work.

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Abstract

Background: We examined the relationship of midlife cardiovascular health (CVH) with late-life robustness among men and women and the impact of survivorship bias on sex differences in robustness.

Methods: Prospective analysis of 15 744 participants aged 45–64 (visit 1 median age: 54 years, 55% female, 27% Black) in 1987–1989 from the population-based Atherosclerosis Risk in Communities Study. CVH was operationalized according to the Life's Simple 7 (LS7) metric of health behaviors (smoking, weight, physical activity, diet, cholesterol, blood pressure, and glucose); each behavior was scored as ideal (2 points), intermediate (1 point), or poor (0 points) and summed. Late-life robust/prefrail/frailty was defined at visit 5 (2011–2013). Multinomial regression estimated relative prevalence ratios (RPRs) of late-life robustness/prefrailty/frailty/death across overall midlife LS7 score and components, for the full visit 1 sample. Separate analyses considered visit 5 survivors-only.

Results: For each 1-unit greater midlife LS7 score, participants had a 37% higher relative prevalence of being robust versus frail (overall RPR = 1.37 [95% confidence interval {CI}: 1.30–1.44]; women = 1.45 [1.36–1.54]; men = 1.24 [1.13–1.36]). Among the full visit 1 sample, women had a similar 1-level higher robustness category prevalence (RPR = 1.35 [95% CI: 1.32–1.39]) than men (RPR = 1.31 [95% CI: 1.27–1.35]) for every 1-unit higher midlife LS7 score. Among survivors, men were more likely to be robust than women at lower LS7 levels; differences were attenuated and not statistically different at higher midlife LS7 levels.

Conclusions: Midlife CVH is positively associated with robustness in late life among men and women. Accounting for mortality in part explains documented sex differences in robustness across all levels of LS7.

Keywords: American Heart Association, Cohort study, Life's Simple 7, Physical function

Frailty is a syndrome of increased vulnerability to stressors thought to reflect declines in physiologic function and reserves across multiple systems (1), encompassing nutrition (unintentional weight loss), weakness, exhaustion, low energy expenditure, and slowness (2–4).

Older adults without any of these features have been described as "robust" (2). Robustness defined within this framework is, in contrast to frailty, associated with more favorable health outcomes, including lower mortality, incident disability, risk of institutionalization, and better postsurgical outcomes (2,4–6).

Demographic projections point to a 27% increase in individuals 65 years and older by 2050 (7), significantly affecting rates of chronic disease, disability, and mortality. These trends are particularly worrisome if increasing numbers of older adults have expanded years of adverse health and disability rather than robust health and functioning (8). Currently, 7% to 10% of older community-dwelling adults meet frailty criteria (9). However, the prevalence of frailty increases with age, affecting up to one-half of adults over age 85, the most rapidly growing segment of the population (10). A paradigm shift is needed, focusing on promoting healthy aging and optimal physical functioning into and throughout late life (11). Identifying modifiable factors that promote late-life physical health will be critical to inform efforts to reduce years spent in disabled states and to improve the overall health of aging populations. This is particularly relevant for women, who experience higher rates of frailty across older age groups and live more years with disability, as compared to men (12). Reasons for higher rates of frailty and disability among older women, despite greater longevity, have not been explained.

Factors associated with being robust compared to frail in older age remain understudied. Cardiovascular health (CVH) may be a key contributor, as poor CVH in midlife (13) and in late life (14) is predictive of worse late-life physical function. However, physical function and frailty are not synonymous terms; physical function can be impaired by deficits in a single system while frailty results from deficits in multiple systems and therefore requires knowledge of simultaneous contributors. The American Heart Association developed recommendations for CVH promotion (15), consisting of 7 health behaviors/factors known as Life's Simple 7 (LS7). The LS7 criteria are prognostic of disease-free longevity, good quality of life, and low health care costs, even after accounting for clinically manifest cardiovascular disease (CVD) (16). LS7, CVD, and CVD risk factors (ie, diabetes, obesity, kidney disease) in late life are related to late-life physical function and frailty (17–19). However, whether LS7 in midlife, when interventions might be more effective, relate to physical robustness in late life remains unknown. Higher rates of CVD (20) and mortality (21) in men are established. Whether poorer midlife CVH and/or earlier mortality in men explains reported differences in late-life frailty rates between men and women, however, is uncertain.

We leveraged over 25 years of follow-up within the Atherosclerosis Risk in Communities (ARIC) Study cohort to (i) examine whether better midlife CVH is associated with a higher prevalence of robustness and lower prevalence of frailty in late life in men and women and (ii) to examine the influence of survivorship bias on reported sex differences in late-life robustness status.

Method

Study Population and Design

The ARIC Study is a community-based prospective cohort of 15 792 men and women aged 45–64 years at baseline (1987–1989), recruited from 4 U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. ARIC was designed to investigate the etiology of atherosclerosis and its clinical sequelae. Detailed information about the ARIC Study has been described (22). We excluded non-Black/non-White participants (n = 48), yielding a sample of 15 744 participants. Participants provided written informed consent and institutional review boards at each site approved the study.

Exposure: Midlife CVH

The LS7 score (0–14 points) is a summary of 7 health behaviors/factors (smoking, body mass index [BMI], physical activity, diet score, total cholesterol, blood pressure, and fasting serum glucose), each scored as ideal (2 points), intermediate (1 point), or poor (0 points) (Supplementary Table 1) (23). As previously described, the composite LS7 and individual component categories (ideal, intermediate, or poor) were available and derived for each participant at the baseline (1987–1989) examination, when all participants were middle-aged (13,23). Briefly, smoking history was based on self-report and defined as current (currently smoking or quit within the past year), former (smoked >100 cigarettes but quit more than 1 year ago), or never smoker. BMI was calculated as measured weight in kilograms divided by height in meters squared. Physical activity was ascertained using the Baecke questionnaire, a standardized interviewer-administered questionnaire (24). Up to 4 leisure-time activities were categorized as light, moderate, or vigorous based on the Compendium of Physical Activities (25). Total minutes/week of light, moderate, and vigorous physical activity were calculated. Diet was measured using a 66-item food-frequency questionnaire. Blood pressure was measured 3 times using a random-zero sphygmomanometer; the average of the second and third measurements were used. Plasma total cholesterol was assayed using a standardized enzymatic method (26), and serum glucose was measured by a hexokinase method.

Outcome: Late-Life Robustness/Prefrail/Frailty

Robustness and frailty assessments were first implemented at ARIC visit 5 (2011–2013, ages 66–90 years) as previously described using assessments of gait speed, grip strength, low BMI/weight loss, low physical activity, and low energy (2,5). The criterion and predictive validities of the phenotype in ARIC and other cohorts have been described (2,4,5). Participants meeting 3 or more criteria were classified as frail; 1–2 criteria defined prefrail; and no criteria defined robust status.

Covariates

All covariates were drawn from ARIC visit 1 and include age, sociodemographic, behavioral, and cardiovascular indicators. Race-field center was categorized as Minnesota Whites, Maryland Whites, North Carolina Whites, North Carolina Blacks, and Mississippi Blacks. Education was categorized as less than high school, high school or equivalent, and any college. Participants who responded "Yes" to "Do you presently drink alcoholic beverages?" were classified as current drinkers. Prevalent heart disease was determined by self-reported history of myocardial infarction; myocardial infarction on electrocardiogram; or history of heart or arterial surgery, coronary revascularization. Prevalent heart failure at visit 1 was based on presence of Gothenburg criteria (27) and evidence of heart failure therapy use.

Diabetes and hypertension, described in Table 1 participant characteristics but not included in the adjustment models, were also collected at ARIC visit 1. Diabetes was defined as fasting glucose ≥ 126 mg/dL or >200 mg/dL nonfasting glucose, self-reported history of physician-diagnosed diabetes, or use of diabetes medication. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medications.

Table 1. Midlife (visit 1) Participant Characteristics Overall and Stratified According to Visit 5 Robust Status, Death, and Loss to Follow-up (*N* = 15 744)

		Visit 1 (1987–1989)	Visit 5 (2011–2013) Robust Status				
		Total	Robust	Prefrail	Frail	Deceased	Lost to Follow-up
		N = 15 744	*n* = 2 634	*n* = 2 781	*n* = 396	*n* = 5 837	*n* = 4 096
Demographics	Age, years	54.2 (5.8)	50.6 (4.4)	52.6 (5.2)	54.3 (5.5)	56.8 (5.5)	53.8 (5.6)
	Women	8 685 (55%)	1 434 (54%)	1 666 (60%)	262 (66%)	2 689 (46%)	2 634 (64%)
	Race: Black	4 266 (27%)	520 (20%)	670 (24%)	102 (26%)	1 843 (32%)	1 131 (28%)
	Education < 12 years	3 754 (24%)	253 (10%)	431 (16%)	98 (25%)	1 977 (34%)	995 (24%)
Life's Simple Seven (7) components	LS7 score (0–14)	7.9 (2.4)	9.2 (2.2)	8.3 (2.3)	7.5 (2.2)	7.0 (2.3)	8.0 (2.3)
	Hypertension	4 640 (30%)	436 (17%)	623 (23%)	124 (31%)	2 315 (40%)	1 142 (28%)
	Systolic BP, mmHg	121.4 (19.0)	114.6 (15.1)	117.1 (15.9)	121.8 (16.7)	126.9 (21.2)	120.6 (17.7)
	Diastolic BP, mmHg	73.8 (11.3)	72.5 (10.0)	72.9 (10.4)	74.3 (11.3)	74.8 (12.5)	73.6 (10.8)
	Hypertension medication	4 833 (31%)	451 (17%)	650 (23%)	138 (35%)	2 401 (41%)	1 193 (29%)
	Total cholesterol, mg/dL	215.0 (42.1)	207.7 (39.3)	212.7 (40.1)	212.6 (38.8)	217.7 (43.7)	217.6 (42.4)
	Cholesterol medication	452 (3%)	50 (2%)	68 (2%)	6 (2%)	208 (4%)	120 (3%)
	Diabetes	1 558 (10%)	63 (2%)	134 (5%)	37 (9%)	1 048 (18%)	276 (7%)
	Fasting glucose, mg/dL	109.0 (40.6)	99.1 (16.5)	102.3 (25.2)	107.6 (37.7)	119.6 (56.0)	105.0 (29.6)
	Diabetes medication	882 (6%)	21 (1%)	59 (2%)	11 (3%)	659 (11%)	132 (3%)
	Physical activity (min/wk)	57.6 (99.7)	80.5 (115.7)	59.6 (100.0)	40.2 (85.2)	49.1 (92.0)	55.2 (97.7)
	Diet score	2.0 (1.0)	2.0 (1.0)	1.9 (1.0)	2.0 (1.0)	1.9 (1.0)	2.0 (1.0)
	Body mass index, kg/m^2	27.7 (5.4)	26.1 (4.1)	27.6 (4.8)	30.0 (6.2)	28.3 (5.8)	27.8 (5.5)
	Current smoker	4 117 (26%)	431 (16%)	509 (18%)	71 (18%)	2 169 (37%)	937 (23%)
Other comorbidities and metrics	Heart failure	751 (5%)	36 (1%)	76 (3%)	16 (4%)	457 (8%)	166 (4%)
	Heart disease	765 (5%)	31 (1%)	63 (2%)	11 (3%)	561 (10%)	99 (2%)
	Stroke	284 (2%)	11 (0.004%)	18 (1%)	9 (2%)	215 (4%)	31 (1%)
	Current drinker	8 742 (56%)	1 733 (66%)	1 608 (58%)	209 (53%)	3 003 (52%)	2 189 (54%)

Notes: BP = blood pressure; LS7 = American Heart Association Life Simple 7. Values are unadjusted mean (standard deviations; *SD*s) or no. (%). To convert values to mmol/L, multiply values for total. Kruskal–Wallis test for continuous variables, Fisher's Exact Test for categorical variables. All p values < .001.

Statistical Analyses

Descriptive analysis used Fisher's Exact Test for categorical variables and Kruskal–Wallis test for continuous variables to examine differences in baseline characteristics across visit 5 robustness status. Multinomial regression models estimated adjusted relative prevalence ratios (RPRs) and 95% confidence intervals (CIs) of late-life 4-level robustness outcomes (robust = 1, prefrail = 2, frail = 3, and death = 4) with respect to midlife LS7 levels (range: 0–14) and individual LS7 component criteria (poor, intermediate, and ideal); marginalized prevalence rates were calculated. Ordinal regression models showed similar probabilities to multinomial models. We additionally used a "conditional on being alive" (survivors-only) approach to estimate RPRs from a 3-level multinomial robustness outcome (excluding death). Since the conditional approach ignores potential effects that CVH has on survivorship into late life, the full population approach better addresses our questions concerning midlife LS7 associations with late-life outcomes. However, contrasting the 2 approaches can offer specific insights into subpopulation differences (such as men and women) when there are differential mortality experiences and allows comparisons to existing literature which has been essentially limited to survivors in older age (28). All models included pooled analyses and analyses stratified by sex. All analyses were adjusted for visit 1 age, sex, educational attainment, race-center, heart failure, heart disease, current drinking status, and stroke. LS7-component predictors were analyzed in both separate models and simultaneously (eg, adjusted for the other LS7 components). Predictive margins following multinomial regression were used to generate estimates and CIs reported in the figures and tables. Analyses were conducted using Stata version 16.0 (StataCorp LP, College Station, TX).

Sensitivity Analyses

Sensitivity analyses with models accounting for nonparticipation were fit using inverse probability weighting (IPW) under missing at random assumptions (29–31). Briefly, weights were derived from a logistic regression model where loss to follow-up was estimated as a

function of all covariates above. All multinomial models were then reestimated incorporating IPW weights to mimic the originating target population.

Results

Participant Characteristics

Baseline (visit 1) demographic and clinical characteristics of the study population by robust status are provided in Table 1. Among the 15 744 participants (median age: 54 years, 55% women, 27% Black), 5 837 died prior to visit 5. Of the 9 907 participants alive at visit 5, 6 520 attended the examination, and 5 811 completed the frailty assessment. The prevalence of robustness was 45.3% (n = 2 634), prefrailty was 47.9% (n = 2 781), and frailty was 6.8% (n = 396). Participants classified as robust in late life were younger, less often female, and had higher educational attainment, fewer comorbidities, better CVH parameters, and higher LS7 levels at midlife compared to the remaining study population (Table 1). Participants who survived to visit 5 (n = 6 520, Supplementary Table 2) were more likely to be women, have higher midlife LS7 levels, lower prevalence of CVD and cardiovascular risk factors, lower blood pressure and cholesterol, and higher levels of physical activity than the visit 1 sample. Supplementary Table 3 includes the distribution of LS7 levels, by sex, in the visit 1 population and among survivors-only. Compared to men, women were more likely to have a greater frequency of LS7 levels between 1–4 and 11–14.

Overall LS7 Associations

Better midlife LS7 levels were associated with better outcomes for every contrast (Table 2). In multinomial models, every 1-unit higher midlife LS7 score was accompanied by a 37% higher relative prevalence of being robust versus frail, RPR = 1.37 (95% CI: 1.30, 1.44), an 18% higher relative prevalence of being robust versus prefrail, RPR = 1.18 (1.15, 1.22), a 16% higher relative prevalence of being prefrail versus frail, RPR = 1.16 (1.10, 1.22), and a 10% higher relative prevalence of being frail versus dying, RPR = 1.10 (1.05, 1.16). Participants were most frequently categorized as ideal in the smoking metric (71% nonsmoking) and the least frequently in healthy diet (only 5%) (Table 2). Relative to poor LS7 metrics, all ideal midlife LS7 metrics were associated with a higher late-life relative prevalence of robust versus prefrail. The largest association was observed for BMI, which showed a 7-fold higher relative prevalence of being robust versus frail with ideal BMI compared to poor BMI, RPR = 7.13 (5.27, 9.65). Forest plots showing pooled and sex-specific analyses across each LS7 component are provided in Supplementary Figure 2. Results were similar for survivors-only (Supplementary Table 4) and in IPW sensitivity analyses (Supplementary Table 5 for full population, Supplementary Table 6 for survivors-only).

Associations by Sex

In sex-stratified ordinal analyses (Table 3), each 1-unit higher midlife LS7 score was similarly associated with a greater likelihood of being in any better outcome category (ie, the association was similar across the following comparisons: robust vs prefrail/frail/death, robust/prefrail vs frail/death, robust/prefrail/frail vs death) for women (RPR = 1.35 [1.32, 1.39]) and men (RPR = 1.31 [1.27, 1.35]), p-interaction = .867. The ordinal assumption eases comparisons across sex; results were also similar for men and women in nonordinal, multinomial models (Supplementary Table 7 [women] and Supplementary Table 9 [men]) and between sex in survivor-only analyses (Supplementary Tables 8 [women] and Supplementary Table 10 [men]).

Figure 1, Panel A1–A3, contrasts the expected prevalence of being late-life robust (A1), prefrail (A2), and frail (A3) over the continuum of midlife LS7 levels among men and women who were alive at visit 5. At low LS7 levels, surviving men were more likely to be robust than surviving women in late life (Figure 1, Panel A1, eg, 40% robust for men vs 29% robust for women at LS7 = 6), but differences were attenuated with overlapping CIs at higher midlife LS7 levels (eg, 63% robust for men vs 58% robust for women at LS7 = 12). The prevalence of robustness, prefrailty, frailty, and death by sex subgroups for each 1-unit LS7 increment is provided for the full visit 1 population and among survivors-only in Supplementary Tables 11 and 12, respectively. Figure 1, Panel B, visually presents prevalences of the 3-level robust categories across LS7 levels within women (B1) and men (B2) among those alive at visit 5. For both men and women, with higher midlife LS7, the prevalence of late-life robustness was greater, while the prevalences for frail and prefrail were lower.

Figure 2 contrasts late-life robustness prevalence estimates between the survivors-only approach (Panel A, excluding deaths) and the full population approach (Panel B, including deaths). While observed late-life robustness was generally higher in men compared to women among survivors (eg, 48% vs 38% at LS7 = 8), late-life robustness was instead similar when considering the full originating sample and including death outcomes (eg, 20% for men vs 22% for women at LS7 = 8).

In the full population approach, which includes those who died (Supplementary Figure 1), nonlinear associations are seen since death has a dramatic influence on frailty and prefrailty prevalence at lower CVH levels. As shown in Supplementary Figure 1, frailty and prefrailty prevalence actually increase in the full population (Supplementary Table 11) as CVH increases at lower LS7 levels, (eg, from LS7 2 to 3 or 3 to 4, etc.), up until around LS7 = 8–9, whereby frailty starts to decrease with additional increases in CVH (eg, from 8 to 9, 9 to 10, etc.). This suggests a clear survivorship effect. Conceptually, when death is considered as a competing future state, improving CVH at very low levels moves individuals from the death category to the frail category. This makes the frailty prevalence increase, but appropriately so since participants who would have died are now "only" frail. These patterns occur up until LS7 around 8–10, where we observe a decrease in all adverse states (death, frail, and prefrail), similar to the patterns shown in the survivors-only analysis. Importantly, robustness rates increase across all levels of increasing CVH, similar to the survivors-only analysis, but now with more appropriate future-predictive prevalences, given that the full starting population is used (including those who go on to die).

Discussion

In this biracial community-based cohort, better midlife CVH was associated with a higher prevalence of being physically robust and having a lower prevalence of frailty in late life. Particularly strong associations were observed for midlife BMI, fasting glucose, physical activity, and blood pressure. Although the lowest risk was evident with ideal levels of CVH, even intermediate levels were associated with better physical robustness. We also found well-established sex differences in late-life robustness prevalences favoring men. The differences we observed in patterns of robustness across LS7 levels by sex among survivors were attenuated

Table 2. Relative Prevalence Ratios (95% confidence intervals) for Midlife (baseline) LS7 Associations With Late-Life Robust Status and Mortality 25 Years Later: The Atherosclerosis Risk in Communities Study 1987–2013 (unconditional, *N* = 15 744)

			Robust vs Prefrail (ref)	Robust vs Frail (ref)	Robust vs Death (ref)	Prefrail vs Frail (ref)	Prefrail vs Death (ref)	Frail vs Death (ref)
LS7 score (per 1-unit increment) (0–14)			1.18 (1.15, 1.22)	1.37 (1.30, 1.44)	1.51 (1.47, 1.55)	1.16 (1.10, 1.22)	1.28 (1.24, 1.31)	1.10 (1.05, 1.16)
Fasting glucose	Poor	11%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	38%	1.54 (1.16, 2.04)	2.23 (1.44, 3.45)	4.14 (3.21, 5.35)	1.45 (0.97, 2.17)	2.69 (2.22, 3.26)	1.86 (1.27, 2.71)
	Ideal	51%	1.81 (1.38, 2.39)	2.78 (1.82, 4.25)	6.14 (4.78, 7.88)	1.53 (1.03, 2.27)	3.38 (2.80, 4.08)	2.21 (1.53, 3.18)
Smoking	Poor	26%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	3%	1.35 (0.94, 1.94)	0.96 (0.50, 1.84)	2.54 (1.81, 3.57)	0.71 (0.37, 1.36)	1.88 (1.36, 2.59)	2.65 (1.43, 4.93)
	Ideal	71%	1.25 (1.08, 1.45)	1.30 (0.97, 1.74)	4.16 (3.62, 4.78)	1.04 (0.78, 1.39)	3.33 (2.94, 3.77)	3.19 (2.42, 4.21)
Blood pressure	Poor	26%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	36%	1.14 (0.96, 1.36)	1.43 (1.07, 1.91)	1.90 (1.62, 2.23)	1.26 (0.95, 1.66)	1.67 (1.46, 1.91)	1.33 (1.02, 1.73)
	Ideal	38%	1.38 (1.17, 1.64)	2.59 (1.91, 3.52)	3.40 (2.90, 4.00)	1.87 (1.39, 2.52)	2.46 (2.14, 2.83)	1.32 (0.99, 1.75)
Body mass index	Poor	28%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	39%	1.56 (1.34, 1.82)	3.49 (2.67, 4.55)	2.49 (2.14, 2.90)	2.23 (1.73, 2.88)	1.60 (1.41, 1.81)	0.71 (0.56, 0.91)
	Ideal	33%	2.50 (2.13, 2.93)	7.13 (5.27, 9.65)	3.50 (2.99, 4.09)	2.85 (2.13, 3.83)	1.40 (1.22, 1.60)	0.49 (0.37, 0.65)
Physical activity	Poor	38%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	25%	1.37 (1.19, 1.59)	1.94 (1.46, 2.58)	1.73 (1.49, 2.00)	1.41 (1.07, 1.86)	1.26 (1.10, 1.43)	0.89 (0.68, 1.17)
	Ideal	37%	1.67 (1.46, 1.92)	2.66 (2.03, 3.49)	2.19 (1.92, 2.51)	1.59 (1.22, 2.08)	1.31 (1.16, 1.48)	0.82 (0.64, 1.07)
Healthy diet	Poor	31%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	64%	1.26 (1.11, 1.43)	1.36 (1.06, 1.74)	1.26 (1.11, 1.43)	1.07 (0.84, 1.37)	1.00 (0.89, 1.11)	0.93 (0.73, 1.18)
	Ideal	5%	1.59 (1.23, 2.06)	1.37 (0.85, 2.22)	1.78 (1.38, 2.30)	0.86 (0.54, 1.39)	1.12 (0.88, 1.43)	1.30 (0.81, 2.06)
Total cholesterol	Poor	27%	-ref-	-ref-	-ref-	-ref-	-ref-	-ref-
	Intermediate	36%	1.13 (0.97, 1.31)	1.03 (0.77, 1.37)	1.36 (1.18, 1.57)	0.91 (0.69, 1.20)	1.20 (1.06, 1.36)	1.32 (1.01, 1.73)
	Ideal	36%	1.20 (1.03, 1.39)	1.05 (0.78, 1.40)	1.33 (1.16, 1.54)	0.88 (0.66, 1.16)	1.11 (0.98, 1.27)	1.27 (0.96, 1.68)

Notes: LS7 = American Heart Association Life Simple 7. Adjusted for age, sex, race-site, educational attainment, heart failure, heart disease, drinking status, stroke. Reported as relative prevalence ratios from 4-category multinomial models (robust, prefrail, frail, or death). Results are from separate models for LS7 score and each separate LS7 component. Predictor -ref- group throughout is poor LS7 component.

Table 3. Relative Prevalence Ratios (95% confidence intervals) for Midlife (baseline) LS7 Associations With Ordinal 4-Level Late-Life Robust Status: The Atherosclerosis Risk in Communities Study 1987–2013 (overall and by sex subgroups, *N* = 15 744)

		Pooled	Women	Men
LS7 score (per 1-unit increment) (0–14)		1.33 (1.30, 1.35)	1.35 (1.32, 1.39)	1.31 (1.27, 1.35)
Fasting glucose	Poor	-ref-	-ref-	-ref-
	Intermediate	2.86 (2.45, 3.34)	3.48 (2.81, 4.30)	2.28 (1.82, 2.85)
	Ideal	3.79 (3.26, 4.40)	4.93 (4.01, 6.05)	2.85 (2.28, 3.56)
Smoking	Poor	-ref-	-ref-	-ref-
	Intermediate	2.06 (1.63, 2.61)	1.75 (1.24, 2.47)	2.42 (1.74, 3.36)
	Ideal	3.03 (2.76, 3.34)	2.81 (2.47, 3.19)	3.39 (2.94, 3.92)
Blood pressure	Poor	-ref-	-ref-	-ref-
	Intermediate	1.68 (1.51, 1.87)	1.88 (1.63, 2.17)	1.46 (1.25, 1.72)
	Ideal	2.54 (2.28, 2.82)	2.90 (2.51, 3.35)	2.21 (1.88, 2.60)
Body mass index	Poor	-ref-	-ref-	-ref-
	Intermediate	1.82 (1.65, 2.00)	1.81 (1.59, 2.07)	1.78 (1.54, 2.06)
	Ideal	2.22 (2.01, 2.46)	2.67 (2.34, 3.05)	1.82 (1.54, 2.14)
Physical activity	Poor	-ref-	-ref-	-ref-
	Intermediate	1.43 (1.30, 1.58)	1.43 (1.26, 1.63)	1.43 (1.23, 1.67)
	Ideal	1.69 (1.55, 1.86)	1.71 (1.51, 1.94)	1.68 (1.46, 1.93)
Healthy diet	Poor	-ref-	-ref-	-ref-
	Intermediate	1.15 (1.06, 1.25)	1.16 (1.02, 1.31)	1.15 (1.02, 1.29)
	Ideal	1.43 (1.20, 1.72)	1.46 (1.17, 1.83)	1.37 (1.00, 1.87)
Total cholesterol	Poor	-ref-	-ref-	-ref-
	Intermediate	1.23 (1.11, 1.36)	1.32 (1.16, 1.50)	1.15 (0.99, 1.34)
	Ideal	1.19 (1.08, 1.32)	1.30 (1.14, 1.49)	1.12 (0.96, 1.30)

Notes: LS7 = American Heart Association Life Simple 7. Adjusted for age, sex, race-site, educational attainment, heart failure, heart disease, drinking status, stroke. Estimates are from ordinal regression models using 4-level robust outcome (robust, prefrail, frail, or death). Results are from separate models for LS7 score and each separate LS7 component. Predictor -ref- group is poor LS7 component. Relative prevalence ratio refers to the chance of being in any categorical outcome relative to the poorer outcome below it (eg, robust vs prefrail, prefrail vs frail, frail vs death). *p*-Interaction of sex and LS7 on robust outcomes = .867.

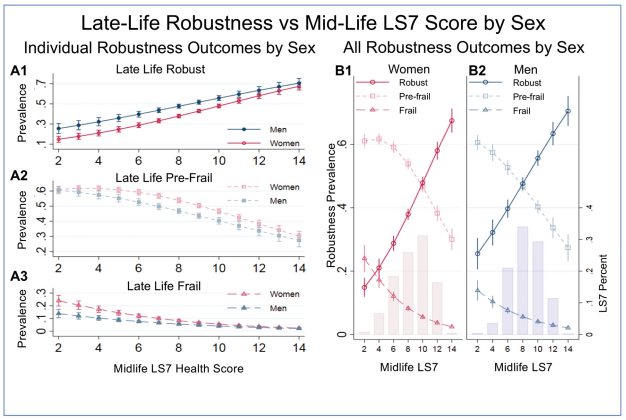

Figure 1. Prevalence of robust (A1), prefrail (A2), and frail (A3) status 25 years later as a function of baseline LS7 levels for women (B1) and men (B2): The Atherosclerosis Risk in Communities Study 1987–2013 (conditional on being alive, *n* = 6 520). Estimates are derived from a conditional on being alive 3-category multinomial regression model adjusting for age, sex, race-site, educational attainment, heart failure, heart disease, drinking status, stroke. Histograms of LS7 categories designated in blue (men) and red (women) with prevalence distribution indicated on the right-hand y-axis as LS7 percent. LS7 = American Heart Association Life Simple 7.

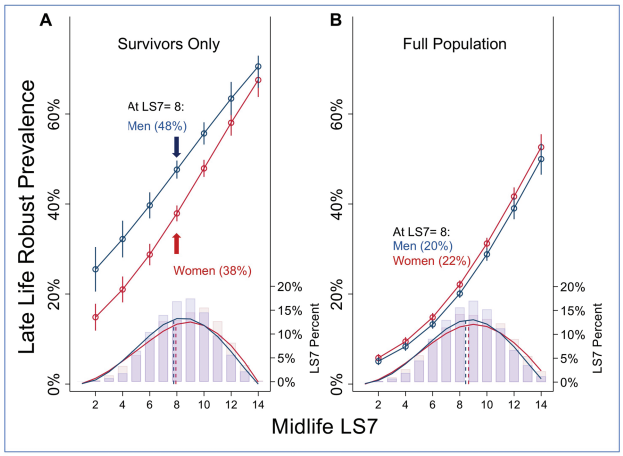

Figure 2. Prevalence of robust status 25 years later as a function of baseline LS7 levels: The Atherosclerosis Risk in Communities Study 1987–2013 (Panel A: conditional on being alive, *n* = 6 520) and (Panel B: full originating population *N* = 15 744). Estimates for Panel A are derived from a conditional on being alive multinomial regression model adjusting for age, sex, race-site, educational attainment, heart failure, heart disease, drinking status, stroke. Histograms of LS7 categories designated in blue (men) and red (women) with prevalence distribution indicated on the right-hand y-axis as LS7 percent. Dashed line = mean LS7 score. LS7 = American Heart Association Life Simple 7.

when adjusting for attrition due to nonparticipation or death. Poorer LS7 levels in men compared to women and accompanying higher mortality in men, especially at lower LS7 levels, may explain some of the documented sex disparities in robustness prevalence in studies of survivors in older age. Results from this study suggest that public health messages and counseling patients during midlife should include potential benefits on physical robustness, avoiding frailty, in addition to cardiovascular outcomes, with an emphasis on maintaining ideal levels of these modifiable risk factors earlier in the life course.

Previous work supports the importance of midlife CVH on late-life outcomes, including mortality, cardiovascular events, and

physical performance (13,32,33). However, the current study findings extend existing work by examining the frailty syndrome as an outcome, which, to our knowledge, has only been previously examined in the prospective Nutrition and Cardiovascular Risk in Spain (ENRICA) Study (28). In this study of 1 745 community-dwelling older adults free of CVD, having >2 ideal LS7 components was associated with a lower frailty incidence, which similar to our study supports the notion that some benefits of CVH on physical frailty may be seen even among those who did not achieve optimal health metrics. Other studies focused on physical performance as an outcome. However, poorer physical performance could be explained by a single system impairment, such as knee arthritis, while frailty is widely believed to encompass dysregulation across multiple physiologic systems. Although a consensus definition of frailty is lacking, multiple lines of evidence support this multisystem conceptualization of frailty. Frailty remains an important outcome because these deficits do not always manifest with clinical disease and disability (34), and may therefore remain undetected by clinicians. Often following comorbidity and disability, the evolution of frailty is unrecognized until late in its course, when interventions are less effective, making prefrailty a particularly important state to intervene upon to prevent adverse outcomes. The observation that frailty was associated with multiple midlife systems in the LS7 framework, incorporating information from the endocrine, energy (dietary intake, obesity), and vascular systems suggests that multi-prong approaches earlier in life focusing on these modifiable factors may help preserve robust function in later life.

Many previous studies were conducted in older adulthood, and may be subject to survivor biases as participants with the poorest midlife lifestyles are less likely to survive to be enrolled into these studies and more likely to have been physically frail. Therefore, associations among survivors likely underestimate benefits of earlier life health factors. Our findings suggest a survivor bias is an important factor in the male–female frailty paradox, in which women live longer lives but have poorer health and greater frailty. Consistently, observational studies support higher mortality among men compared to women, yet higher frailty among older women (12). The prospective nature of this study from midlife sheds new light on these sex disparities in 2 ways. First, we demonstrated that disparities between men and women in rates of robustness and frailty were significantly reduced when men and women had equally ideal (high LS7 levels) CVH in *midlife*. Second, we found that higher death rates in men, associated with poorer CVH in midlife, also explained at least some of the differences in late-life frailty rates between men and women. Our findings in which the sex disparity in prevalence of being robust among older adults was attenuated when accounting for mortality also emphasize the importance of considering survivorship bias to better understand this paradox.

There are some limitations to this study. First, attrition biases are of concern in any longitudinal study; those who drop out may have poorer CVH and be frailer. We addressed this in 2 ways: we incorporated deaths and attrition as an outcome, and we included sensitivity analyses using IPW weights. The latter provided similar results, but there might always exist additional informative missingness bias. Second, we did not examine changes in the LS7 components given a lack of available data on all components at all follow-up visits. However, our focus in this manuscript was to test the association of *midlife* CVH with frailty. All participants were middle-aged only at ARIC visit 1 (1987–1989, 45–64 years). Third, the physical activity component of LS7 is also a component of the frailty outcome. However, the LS7 exposure and the frailty outcome are separated by ~25 years; a moderate correlation ($r = 0.39$) between midlife and late-life physical activity is unlikely to have had a significant influence on observed relationships. Additional limitations include our lack of information on baseline frailty status, time to frailty event data, and insufficient information on the timing of frailty onset in relation to death. Finally, residual confounding remains a possibility, and we cannot infer causality between LS7 and robustness. However, the prospective study design provides additional support for a causal association. Despite these limitations, several strengths should be noted, including the measurement of cardiovascular exposures in midlife, a critically important window for late-life aging-relevant health outcomes, the prospective design with extensive 25-year follow-up, and objective measures of frailty in late life, thus reducing the potential for misclassification or overestimation of function in frailty components.

Given the evidence supporting the impact of frailty on morbidity and mortality (35,36), our data support the need for a population-based approach using education, policy, or environmental changes on multiple modifiable factors, particularly BMI, fasting glucose, physical activity, and blood pressure, early in life to increase the chances of compressing morbidity in aging populations and cultivating greater proportions of robust older men and women globally.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

B.G.W. served on the Editorial Board for *Journals of Gerontology*. The other authors declare no conflict of interest.

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